Influence of Injury Pattern on Incidence and Severity of Posttraumatic Inflammatory Complications in Severely Injured Patients

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Abstract

Background: Severe trauma causes systemic inflammatory response syndrome (SIRS) which may lead to multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF). The aim of this study was to evaluate the influence of the injury pattern on the incidence and severity of SIRS, sepsis, MODS, and mortality.

Methods: A total of 1,273 patients with an injury severity score (ISS) of ≥ 9 points and survival of more than 3 days were included in this retrospective study. Outcome parameters were various grades of SIRS, sepsis, MODS, and mortality.

Results: Severe non-infectious SIRS occurred in 23%, sepsis in 14%, and severe MODS in 14% of the patients. Serious (abbreviated injury scale (AIS) ≥ 3 points) head injury and the ISS represented the most potent risk factors for severe SIRS. As estimated by multivariate logistic regression analysis, the presence of severe extremity and pelvic injuries, the ISS, and the male gender were found to be independent risk factors for sepsis. Severe injuries of the abdomen were associated with an increased risk for sepsis in the univariate analysis. Severe injuries to the head or abdomen, the ISS, and the male gender represented independent risk factors for the development of severe MODS. Regarding the late (> 3 days after trauma) hospital mortality, severe head injury, the ISS, and the patient's age were independent risk factors.

Conclusions: Head injury predominantly determines the incidence of non-infectious systemic inflammation, MOF, and late hospital mortality of patients with severe trauma. Skeletal or abdominal injuries represent relevant risk factors for septic complications. Thus, the incidence of posttraumatic, life-threatening inflammatory complications is related with certain injury patterns in addition to the gender and the severity of trauma.

Key Words

Polytrauma · Studies on organ failure · Thorax and abdominal trauma · Traumatic brain injury · Inflammatory response to injury

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Introduction

In the last decade, several studies have shown an increase in hospital trauma deaths and a decrease in prehospital mortality due to more rapid patient transport with diminished scene time [1–3]. While immediate and early trauma deaths are predominantly determined by brain injuries and hemorrhagic shock, late mortality (> 72 h after trauma) is caused by inflammatory complications [1, 4–7]. Severe tissue trauma and particularly

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hemorrhagic shock cause systemic inflammation and represent the main pathophysiologic factor for aseptic systemic inflammatory response syndrome (SIRS) [8–13]. Continued SIRS can result in multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) [9, 11, 14–17].

Recent studies clearly indicated that SIRS is frequent in the posttraumatic period [9, 12, 13]. The clinical significance of this syndrome was mainly evaluated in heterogeneous patient populations in the intensive care unit (ICU) [12, 18–21]. Only a few studies evaluated the prognostic value of SIRS assessed at the time of admission, but not the injury pattern to predict early MODS (< 72 h after trauma), mortality, or length of hospital stay [13, 22–24]. In addition, a high injury severity score (ISS) [25] was previously described as a risk factor for the development of posttraumatic inflammatory complications and mortality [2, 13, 26, 27]. However, no data are yet available on the clinical relevance of the injury pattern with regard to incidence and severity of SIRS compared to septic complications and posttraumatic MODS. Therefore, in this study the injury pattern was correlated with the incidence and severity of SIRS, sepsis, and MODS, as well as mortality in critically injured patients in a retrospective study.

Materials and Methods

Patient Selection and Management

The study population included 1,273 injured patients who were admitted to the Division of Trauma Surgery (level I trauma center), University Hospital Zurich, from January 1991 to February 1996. Inclusion criteria were an ISS [25] ≥ 9 points [28], patient age > 16 years, less than 4 h between accident and hospital admission, surveillance on the ICU and survival of more than 3 days. All patients were treated according to the advanced trauma life support (ATLS) guidelines [29] and our standard trauma protocol [30–32]. In brief, after control of airway, ventilation, and monitoring of cardiovascular functions, life-saving procedures including decompression of body cavities, control of hemorrhage and contamination were carried out. This was followed by radical wound debridement, decompression of compartments, and primary stabilization of major fractures mostly through external fixation ("day one surgery") [30, 31]. Thereafter, patients were transferred to the ICU for restoration of organ functions. Of note, all patients received enteral nutrition within 24 h after trauma to maintain normal intestinal flora and bowel mucosa [33]. Antibiotics were only used, if a septic focus was verified by a positive bacterial culture.

Definition of Isolated Injuries, Multiple Injuries, and Polytrauma

A severe isolated injury was defined as an injury with an abbreviated injury scale (AIS) [25] of ≤ 3 points and at most one additional injury with an AIS of ≤ 2 points [28, 34]. As a modification of the ISS [25], facial injuries were classified and graded as head injuries. Multiple injuries were defined as a combination of injuries resulting in a total ISS of more than 17 points [35]. In addition, the term polytrauma was defined as a syndrome of multiple injuries (ISS > 17 points) with consequent SIRS for at least one day leading to dysfunction or failure of remote organs and vital systems, which had not themselves been directly injured [35].

Definition of Systemic Inflammatory Response Syndrome

Clinical data including laboratory and vital parameters were prospectively collected. The occurrence of SIRS, sepsis, and MODS was retrospectively analyzed using the prospectively collected parameters. SIRS was defined according to the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [8]. The described criteria were modified, inasmuch as they had to be fulfilled at least for three continuous days to allow the diagnosis of SIRS or sepsis, respectively [26, 27]. SIRS was graded into SIRS 2 (two positive criteria, moderate SIRS) and SIRS 3/4 (three or four positive criteria, severe SIRS) [12, 26, 27]. Sepsis was diagnosed, if all four criteria of SIRS were met for at least 3 days in the presence of a septic focus with positive bacterial tissue culture or a positive blood culture [26, 27].

Definition of Multiple Organ Dysfunction Syndrome

MODS was defined according to the MOF score of Goris et al. [15] including our modifications [14, 26, 27]. Since this score was initially created for critically ill patients independent of the pathogenesis and the underlying disease, criteria for the gastrointestinal tract and the central nervous system were changed in line with our therapeutical strategies for severely injured patients [30, 31, 35]. Accordingly, partial enteral nutrition and requirement of neuromonitoring were specified as organ dysfunction (1 point), while total parenteral nutrition and therapy of intracranial pressure were defined as failure (2 points) of the respective organ system [14]. The criteria had to be met for at least three continuous days. MODS was graded in three groups: MODS I (mild): $> 0 \leq 2$ points, MODS II (moderate): $> 2 \leq 5$ points, and MODS III (severe): > 5 points. The term MOF [15] corresponds to severe MODS according to previous studies [26, 27].

Presentation of Data and Statistics

Results are presented as means and standard deviation (mean ± SD). Continuous data were analyzed by nonparametric Mann–Whitney rank sum test. Categorical variables were compared by χ^2 test. Differences were considered significant, if p values were less than 0.05. For comparisons within injury patterns (head, thorax, abdomen, extremities, pelvis, and spine), a Bonferroni correction was applied. Thus, p values less than $0.05/6 = 0.008$ were considered significant. Logistic regression analysis was performed to test age, gender, injury patterns as independent risk factors for posttraumatic complications and mortality. Statistical analysis was performed using the SPSS software package (SPSS 11.0 for Macintosh).

Results

Demographic Data of Study Population

A total of 1,273 (males, n = 913; females, n = 360) injured patients were included in this study according to the above-mentioned criteria. Of all patients, 67.6% had severe isolated injuries, 32.4% sustained multiple injuries. The mean age, ISS, Glasgow coma scale (GCS), acute physiology and chronic health evaluation (APACHE) II score [36] and ICU stay as well as the percentage of males of the patients with severe isolated or multiple injuries are listed in Table 1.

Incidence of Posttraumatic Complications and Mortality after Isolated or Multiple Injuries

Severe SIRS (3 or 4 criteria fulfilled) occurred in 22.8% of patients and sepsis in 13.8% (Table 2). Patients with severe multiple injuries showed a significantly ($p < 0.05$) higher rate of severe SIRS and sepsis than patients with severe isolated injuries (Table 2).

A severe MODS was observed in 13.5% of all included patients in the posttraumatic course. The incidence of moderate or severe MODS was significantly higher in patients with multiple injuries compared to patients with isolated injuries (Table 2).

The mortality rate of all patients was 7.1%. Patients with multiple injuries had a slightly higher (8.5%) – but not significant – mortality than patients with isolated injuries (6.5%) (Table 2).

Association between Injury Pattern and SIRS or Sepsis

Further, we assessed the influence of one severely injured anatomic region on the incidence and severity of SIRS or sepsis. In patients with severe isolated head injuries, the incidence of severe SIRS was 30.6%, whereas patients with other isolated injuries developed severe SIRS in only 12.9% (Figure 1a). The rate of septic complications was significantly higher in patients with other severe isolated injuries than

Table 1. Demographic data of included patients. ISS: injury severity score [25]; GCS: Glasgow coma scale; APACHE II: acute physiology and chronic health evaluation II [36]; ICU: intensive care unit.

Parameter	All	Isolated injuries	Multiple injuries
Number	1,273	860 (67.6)	413 (32.4)
Age (year)	41.2 ± 18.4	42.2 ± 18.8	39.1 ± 17.4
Males	913 (71.7)	614 (71.4)	299 (72.4)
ISS (points)	19.5 ± 10.3	15.4 ± 6.5	28.0 ± 17.4[a]
GCS (points)	12.2 ± 4.2	12.7 ± 3.9	11.2 ± 4.6[a]
APACHE II (points)	13.2 ± 7.2	12.3 ± 6.9	15.2 ± 7.2[a]
ICU (days)	9.5 ± 10.9	7.8 ± 9.9	12.9 ± 12.2[a]

Mean ± SD. Values in parentheses are percentages

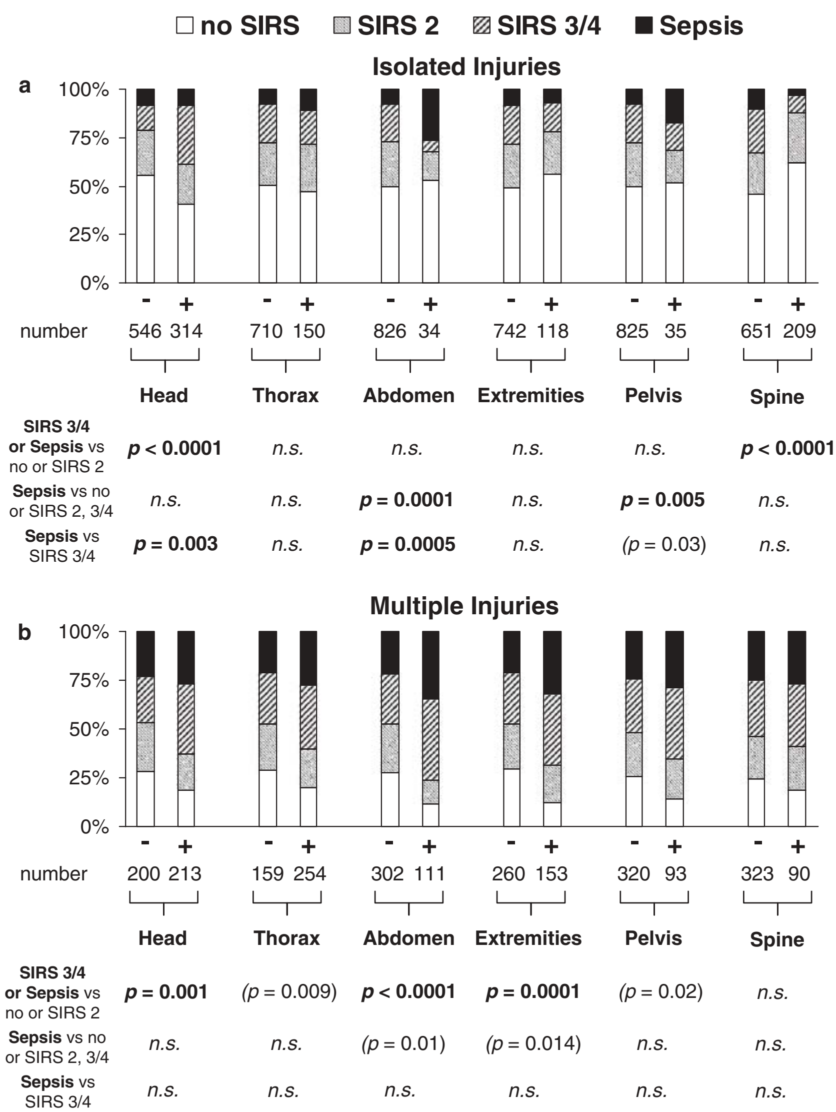
[a] $p < 0.05$ multiple versus isolated injuries

Table 2. Incidence of posttraumatic complications of included patients. SIRS: systemic inflammatory response syndrome [8]; MODS: multiple organ dysfunction syndrome [15].

Parameter	All (n = 1273)	Isolated injuries (n = 860)	Multiple injuries (n = 413)
No SIRS	525 (41.2)	429 (49.9)	96 (23.3)[a]
SIRS 2 (moderate)	282 (22.2)	193 (22.4)	89 (21.5)
SIRS 3/4 (severe)	290 (22.8)	166 (19.3)	124 (30.0)[a]
Sepsis	176 (13.8)	72 (8.4)	104 (25.2)[a]
No MODS	558 (43.8)	455 (52.9)	103 (24.9)[a]
MODS I (mild)	201 (15.8)	137 (15.9)	64 (15.5)
MODS II (moderate)	342 (26.9)	184 (21.4)	158 (38.3)[a]
MODS III (severe)	172 (13.5)	84 (9.8)	88 (21.3)[a]
Mortality	91 (7.1)	56 (6.5)	35 (8.5)

Values in parentheses are percentages

[a] $p < 0.05$ multiple versus isolated injuries



Figures 1a and 1b. Incidence of moderate (SIRS 2), severe (SIRS 3 or 4) systemic inflammatory response syndrome and sepsis in patients with severe (AIS ≥ 3 points) isolated injuries (n = 860) (**a**) or multiple injuries (n = 413) (**b**) in absence (-) or presence (+) of each injured anatomic region (number: number of patients). Data represent percentages. Indicated p values represent significant injury pattern in univariate analyses (χ^2 test); p values < 0.05 in parentheses are not significant after Bonferroni correction; n.s. = not significant.

head injuries with the highest rates in patients with severe isolated abdominal (26.5%) and pelvic (17.1%) injuries (Figure 1a). Patients with severe penetrating abdominal injuries (n = 16, AIS 4.6 points) showed a higher incidence of sepsis (n = 6, 38%) than patients with blunt (n = 18, AIS 4.2 points) abdominal injuries (n = 3, 17%).

To further assess the influence of different anatomic regions on posttraumatic inflammatory complications, the incidence of SIRS and sepsis were evaluated in patients with multiple injuries with regard to each severely (AIS ≥ 3 points) injured anatomic region. Severe SIRS was more frequent in patients with severe head, thoracic, abdominal, extremity, or pelvic injuries compared to patients with spine injuries (Figure 1b). Septic complications were observed most frequently in patients with abdominal or extremity injuries, however not significant after Bonferroni correction (Figure 1b).

Association between Injury Pattern and MODS

Similarly, the incidence of different grades of organ dysfunctions was calculated for severe isolated and multiple injuries. For isolated injuries, the highest rate of severe MODS was observed in patients with head injuries (19.4%), whereas patients with thoracic, extremity, or spine injuries developed less severe MODS (Figure 2a).

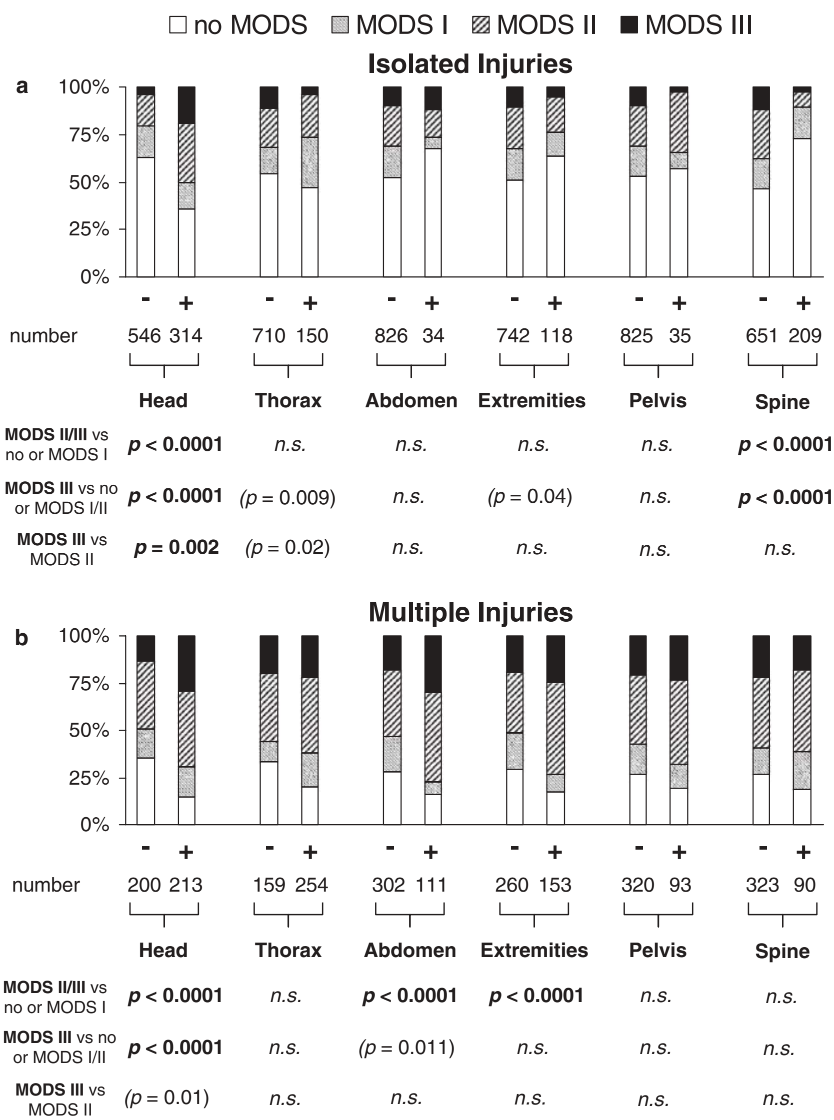
For patients with multiple injuries, severe head, abdominal or extremity trauma caused significantly higher rates of moderate or severe MODS compared to patients without these injuries (Figure 2b).

Association between Injury Pattern and Mortality

In addition, late hospital mortality was evaluated in patients with isolated or multiple injuries. The highest mortality was found in patients with severe isolated head injuries (11.8%), whereas mortality of patients with isolated severe extremity or spine injuries was significantly lower (Figure 3a). Patients with multiple injuries and head trauma had a significantly higher mortality than multiple injured patients without head trauma, whereas other anatomical regions had no influence on mortality rate (Figure 3b).

Association between Injury Pattern and Cause of Death

Causes of death in the 91 patients included MOF (49%), brain edema (41%), pulmonary embolism (6%), and



Figures 2a and 2b. Incidence of mild (MODS I), moderate (MODS II), and severe (MODS III) multiple organ dysfunction syndrome in patients with severe (AIS ≥ 3 points) isolated injuries (n = 860) (**a**) or multiple injuries (n = 413) (**b**) in absence (-) or presence (+) of each injured anatomic region (number: number of patients). Data represent percentages. Indicated p values represent significant injury pattern in univariate analyses (χ^2 test); p values < 0.05 in parentheses are not significant after Bonferroni correction; n.s. = not significant.

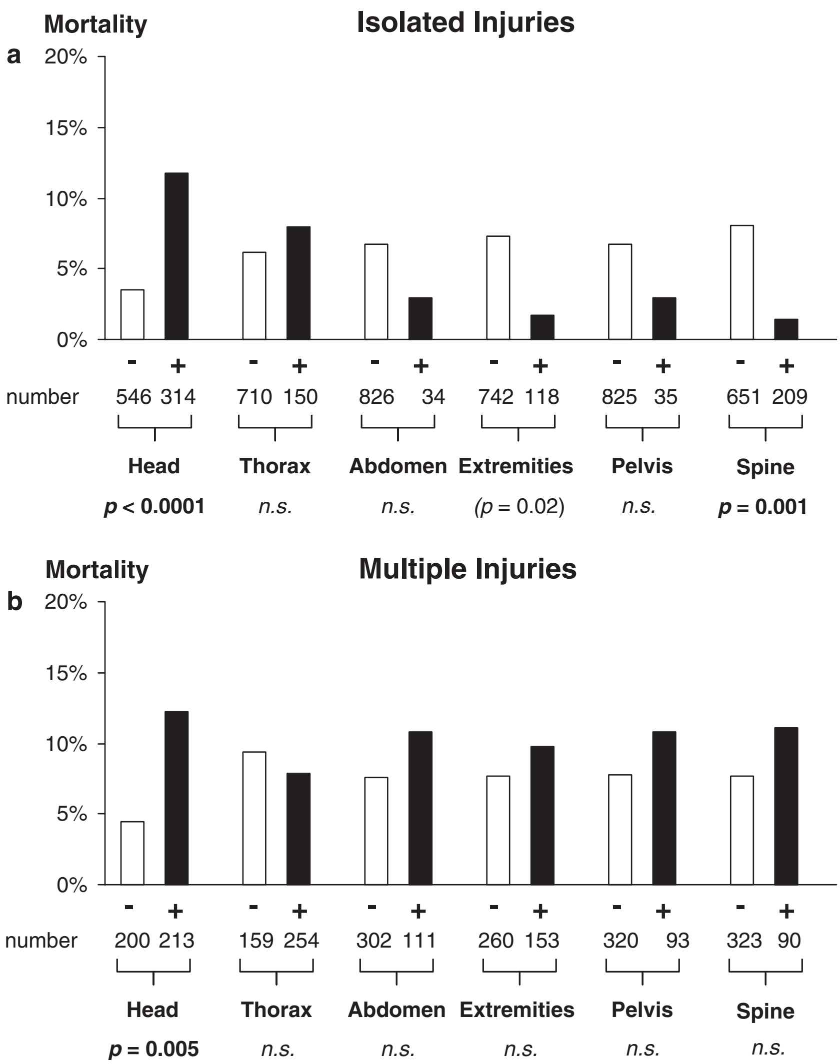
cardiac infarction (4%). In patients with isolated severe head injuries causes of death were MOF in 27% and brain edema in 73%. In patients with multiple injuries and head trauma, MOF represented in 58%, brain edema in 38%, and pulmonary embolism in 4% the causes of death. In contrast, patients with isolated injuries and without head trauma died from MOF in 68%, pulmonary embolism in 16%, and cardiac infarction in 16%. Patients with multiple injuries, but without head injury died in 78% from MOF, in 11% from pulmonary embolism, and in 11% from cardiac infarction.

Relationship between Injury Pattern and Posttraumatic Complications

To identify specific injury patterns as independent risk factors for SIRS, sepsis, severe MODS, and mortality, a multivariate logistic regression analysis was carried out for all 1,273 patients. In the same analysis, age, gender, and ISS were evaluated as further potential risk factors (Table 3). The ISS and severe (AIS ≥ 3 points) head injuries were the most potent, independent risk factors for severe SIRS, sepsis included. Severe thoracic, abdominal, extremity, and pelvic injuries as well as male gender represented further independent risk factors for systemic inflammation. Severe extremity and pelvic injuries, male gender, and the ISS were significant relative risk factors for sepsis, whereas severe abdominal injury represented an independent risk factor for sepsis after exclusion of the ISS in the mulitvariate logistic regression analysis (data not shown). Severe head or abdominal injuries, male gender, and ISS were independent risk factors for severe MODS. Severe head injury, age, and the ISS were independent risk factors for a fatal outcome (death).

Discussion

As known from previous studies [12, 13, 16–18, 26], the severity of injury, estimated by the ISS [25], and the gender determine the incidence of posttraumatic complications such as SIRS, sepsis, MODS, or mortality. Furthermore, the results of this retrospective study demonstrate that the injury pattern influences the late (> 72 h after trauma) posttraumatic morbidity and mortality after severe mechanical trauma. Patients with severe head trauma revealed a significantly higher risk for severe systemic inflammation



Figures 3a and 3b. Mortality rate in patients with severe (AIS ≥ 3 points) isolated injuries (n = 860) (**a**) or multiple injuries (n = 413) (**b**) in absence (-) or presence (+) of each injured anatomic region (number: number of patients). Data represent percentages. Indicated p values represent significant injury pattern for mortality in univariate analysis (χ^2 test); p values < 0.05 in parentheses are not significant after Bonferroni correction; n.s. = not significant.

and multiple organ dysfunctions than patients with other injury patterns. Furthermore, head injuries represented the sole significant lethal factor in the late posttraumatic period, while severe head injury and hemorrhagic shock are the major lethal factors during the first 3 days after trauma [7]. In contrast, abdominal trauma determined septic complications in isolated and in multiple injured patients and increased the risk for MODS, but had no influence on mortality. In addition, extremity and pelvic injuries increased septic complications in multiple injured patients.

Despite the more restricted definition for SIRS in this study, the incidence of SIRS without infection (45%) is higher compared to the study of Rangel et al. (38%) or Malone et al. (29%) [12, 24]. In contrast, the rate of septic complications (13.8%) was lower than in the study of Rangel et al. (30%) [12]. These discrepancies could be explained by the different patient selection. In the present study, patients were only included, if the ISS was ≥ 9 points, the age ≥ 16 years, if the delay from injury to admission was less than 4 h, and if the patients survived more than 3 days to evaluate the late (> 72 h) systemic inflammation. In contrast, the patient collective in the study of Rangel was more heterogenous [12], and in the study of Malone only the SIRS score was taken into account on admission [24]. Additionally, penetrating injuries (8%, data not shown), which are known for a high rate of septic complications, were less frequent in the presented study than in others [4, 5, 24].

The mortality of all patients including those patients, who died within the first 3 days after trauma, was lower (16%, data not shown) compared to the studies by van der Sluis et al. (26%) [34] and Regel et al. (22%) [16, 17]. The early (≤ 3 days after trauma) (9.5%, data not shown) as well as the late (7.1%) posttraumatic mortality rates here were lower than in studies by Acosta et al. (18.9%) [4] and Smail et al. (14.7%) [13]. These discrepancies are possibly due to a more efficient prehospital and hospital management of severely injured patients with shorter transfer times (≤ 4 h after trauma) and more effective surgical and intensive care therapy concepts [14, 26, 30–33].

The presented data are in line with previous observations describing the relevance of coexisting extracranial injuries for the development of infectious problems in patients with severe head injuries [6, 37]. However, in those studies, the incidence of systemic inflammation (SIRS) without infectious focus was not evaluated [6,

Table 3. Multivariate logistic regression analysis of all 1,273 severely injured patients for posttraumatic complications. ISS: injury severity score [25]; AIS: abbreviated injury scale [25]; SIRS 3/4: severe systemic inflammatory response syndrome [8]; MODS III, severe multiple organ dysfunction syndrome [15]; OR: odds ratio; CI: confidence interval; n.s.: not significant.

Risk factors	SIRS 3/4 or Sepsis		Sepsis		MODS III		Death	
	OR	CI	OR	CI	OR	CI	OR	CI
ISS (points)	1.07	1.05–1.09	1.06	1.04–1.07	1.04	1.02–1.06	1.06	1.04–1.08
Head (AIS ≥ 3 points)	2.48	1.80–3.41		n.s.	3.92	2.65–5.80	2.74	1.70–4.43
Thorax (AIS ≥ 3 points)	1.42	1.03–1.97		n.s.		n.s.		n.s.
Abdomen (AIS ≥ 3 points)	1.89	1.17–3.06		n.s.	1.93	1.11–3.34		n.s.
Extremities (AIS ≥ 3 points)	1.80	1.29–2.52	1.47	1.01–2.15		n.s.		n.s.
Pelvis (AIS ≥ 3 points)	2.01	1.30–3.10	1.86	1.17–2.93		n.s.		n.s.
Age (years)		n.s.		n.s.		n.s.	1.03	1.02–1.04
Gender (male)	1.41	1.05–1.09	1.62	1.08–2.43	1.90	1.22–2.94	n.s.	

37]. The high rate of severe SIRS in patients with isolated or combined severe head injuries can be explained by a systemic overwhelming release of proinflammatory mediators which can lead to severe organ dysfunctions [38–40]. In addition, intracranial lesions are responsible for disturbed endocrine functions after severe head injuries which may also be involved in the systemic inflammatory processes and organ dysfunctions [41–43]. Furthermore, it can be speculated that secondary brain damage with increased rate of cell death may be responsible for local as well as systemic inflammatory processes [44, 45]. It is therefore conceivable that aggressive management of head injuries with the aim of limiting secondary brain damages could influence systemic inflammatory response after head injury with a decrease of extracranial complications such as MODS.

Patients with severe abdominal injuries demonstrated a high risk for septic complications and severe MODS. Sepsis in patients with isolated abdominal injuries was frequently combined with penetrating injuries. Pneumonia (70%) and peritonitis (30%) represented the septic foci in multiple injured patients with abdominal trauma (data not shown). These data are supported by previous studies identifying abdominal injuries as an important risk factor for early onset pneumonia and frequent pulmonary organ dysfunctions [17, 46–48]. The significance of extraabdominal septic complications of abdominal injuries was also supported by findings from a mouse model in which pulmonary vascular permeability was experimentally increased [49]. In addition, in the previous studies bacterial translocation was suggested to be a possible pathophysiologic motor of systemic inflammation after severe trauma and was dependent on the efficacy of shock therapy [50, 51].

The data in the presented study further emphasizes the relevance of extremity trauma in multiple injured patients and pelvic trauma in isolated injured patients for the incidence of septic complications. The rate of local infectious complications leading to sepsis was low (16.3%, data not shown), whereas pneumonia predominated (67.3%, data not shown). These data are in line with experimental studies observing altered immune functions and increased susceptibility to gut-derived sepsis following bone and soft-tissue injury [52–54]. Furthermore, severe skeletal injuries such as severe pelvic injuries associated with hemorrhagic shock increased the susceptibility for septic complications [6, 55, 56].

The different rates of severe systemic inflammations and sepsis can be further explained by a variable response of the local and systemic immune system in dependence of the injury pattern. Previous studies [40, 57–61] clearly demonstrate an association between severity of injury and the degree of altered immune functions and support this hypothesis. In addition to injury pattern and severity of injury, the gender-specific dimorphism of immune functions may be essential for the development of septic complications [26]. However, the outcome in the late posttraumatic period as shown in this study seems to be determined by the severity of head injury, whereas abdominal or extremity injuries complicate the posttraumatic course with a long ICU or hospital stay, combined with an increase of costs, but did not influence the late mortality rate. Death of severely injured patients is determined by the severity of head injury and the secondary brain damage. The head injury remains the most important lethal factor. In line with previous studies, the ISS and age represent additional risk factors for death [2, 5, 26].

In summary, the incidence of life-threatening inflammatory complications during the posttraumatic course can be associated with certain injury patterns. Although severe abdominal or extremity trauma represent risk factors for posttraumatic septic complications in multiple injured patients, the successful treatment of severe head injury represents the hallmark for survival of multiple injured patients with head injuries not only in the early but also in the late posttraumatic period. Furthermore, the severity of injury as calculated by ISS is the most potent predictive value for the posttraumatic inflammatory course and outcome.

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